

Remarks

1. Status of the Claims

Claim 1 has been amended to recite the phrase “rare restriction site.” Support for this amendment is found in the specification as filed at least at paragraphs [0199], [0498], [0500], and [0779] (Example 13). Thus, the amendment does not introduce new matter.

Claims 3, 6, 10, 12-14, 17, 19-22, 24-25, 27, 29, 31-35, 37-38, 40-42, 45-48, 50-53, 55-56, 61, 63-79, and 81-101 were previously canceled.

Claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57-60, 62, 80, and 102-104 are pending.

2. Rejection of claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57, 59, 60, 62, 80, 102, and 104 under 35 USC § 103 based on Delcardayre in view of Peterson

The Office has rejected claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57, 59, 60, 62, 80, 102, and 104 as obvious based on Delcardayre et al. (WO 98/31837) (“Delcardayre”) in view of Peterson et al. (US Patent No. 5,783,431) (“Peterson”). Applicants respectfully disagree and traverse the rejection.

Applicants’ invention, as claimed, is directed toward methods of mixing heterologous genes in expression cassettes located on artificial chromosomes, in which the artificial chromosomes comprise concatemers with a nucleotide sequence of the general formula:

$$[rs_2\text{-}SP\text{-}PR\text{-}X\text{-}TR\text{-}SP\text{-}rs_1]_n$$

wherein rs_1 and rs_2 together comprise a rare restriction site, denoted $rs_1\text{-}rs_2$, comprising a recognition sequence of 7 to 38 bases where substantially all restriction sites are complete restriction sites recognized by the same enzyme. See, for instance, claim 1. As noted at paragraph [0498] of the specification, “restriction sites having 7 or more non N bases in the recognition sequence are generally known as “rare restriction sites.” Furthermore, the specification states at paragraph [0199] that “according to the present invention the enzyme specific for the $rs_1\text{-}rs_2$ restriction site is preferably a rare cutter therefore the likelihood of cutting

host genomic DNA fragments with a size similar to the size of the expression cassettes is very limited,” and at paragraph [0500] that “according to a preferred embodiment of the invention, the second restriction site, RS2 and RS2' comprises a rare restriction site. Thus, the longer the recognition sequence of the rare restriction site the more rare it is and the less likely is it that the restriction enzyme recognising it will cleave the nucleotide sequence at other—undesired—positions.”

Neither Delcardayre nor Peterson alone or in combination teach or suggest the Applicants' claimed method of mixing heterologous genes in expression cassettes located on artificial chromosomes.

As stated in Chapter 706.02(j) of the MPEP:

“To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.” *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

Here, Delcardayre (the primary reference) is cited for teachings relating to shuffling methods using artificial chromosomes in yeast. However, the Office concedes on p. 3 of the Office Action that “Delcardayre et al. do not teach an expression cassette comprising the general formula [rs₂-SP-PR-X-TR-SP-rs₁]_n” as recited in claim 1. Neither does Delcardayre disclose or suggest the element of independent claim 1 that “rs₁ and rs₂ together comprise a rare restriction site...comprising a recognition sequence of 7 to 50 bases.”

Peterson fails to cure the deficiencies of Delcardayre. The Office has asserted that Peterson discloses “a method of preparing vectors for expression libraries by linking multiple gene cassettes comprising (5'-3') a promoter, an expressible sequence, and a terminator,” and that “it would have been obvious to an ordinary skill [*sic*] in the art to make concatemers comprising the general formula [rs₂-SP-PR-X-TR-SP-rs₁]_n as demonstrated by Peterson et al.” However, nowhere does Peterson expressly or impliedly suggest the element of independent claim 1 that “rs₁ and rs₂ together comprise a rare restriction site...comprising a recognition sequence of 7 to 50 bases.” While the Office has asserted that Peterson discloses an example wherein rs₁ and rs₂ together form an *MboI* restriction site (at the top of p. 4 of the pending Action), nowhere does Peterson teach or suggest the use of a rare rs₁-rs₂ restriction site having 7

or more non-N bases in the recognition sequence, as claimed and as disclosed in the instant specification.

Peterson discloses the use of a rare restriction site only in a linker joining a concatemer to a solid support and, in fact, teaches away from Applicants' claimed invention. As stated at col. 36, lines 13-17 of Peterson:

When concatenation is completed, the concatemers are released by incubation with a restriction enzyme, such as an intron nuclease, that cleaves a unique and very rare site adjacent to the solid phase to reduce the probability of cleaving the concatenated DNA. (Emphasis added.)

Peterson thus teaches the use of a rare restriction site to **prevent** subsequent cleavage between concatenated cassettes.

In direct contrast, the recited concatamers of the instant claims include a rare restriction site between the cassettes so that the concatemers may be advantageously recognized and cleaved by the same enzyme to release the individual cassettes. Contrary to Peterson's teachings, cleavage of the concatemers in Applicants' invention is desirable, as discussed above, because the excised expression cassettes may be subsequently re-assembled to produce new concatemers having novel combinations of selected expression cassettes. See, for example, paragraph [0199] of the instant specification. Thus, the instant claims relate to the use of rare restriction sites to **facilitate** subsequent cleavage between concatenated cassettes.

As stated in MPEP Chapter 2143.01, "The mere fact that references can be combined or modified does not render the resultant combination obvious unless **>the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385, 1396 (2007)." Here, the mere combination of the disclosures of Delcardayre and Peterson cannot render the combination obvious, precisely because Peterson **teaches away** from the use of rare restriction sites **between** cassettes in a concatemer.

One skilled in the art would not have been motivated to make and use Applicants' invention with any expectation of success because Delcardayre and Peterson, alone or in combination, fail to expressly or impliedly suggest all elements of the claimed invention, and because Peterson teaches away from the claimed invention. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57, 59, 60, 62, 80, 102, and 104 under 35 USC § 103 based on Delcardayre in view of Peterson.

3. Rejection of claim 58 under 35 USC § 103 based on Delcardayre in view of Peterson and further in view of Miao

The Office has rejected claim 58 as obvious based on Delcardayre et al. (WO 98/31837) (“Delcardayre”) in view of Peterson et al. (US Patent No. 5,783,431) (“Peterson”), and further in view of Miao et al. (US 7,351,813) (“Miao”). Applicants respectfully disagree and traverse the rejection.

Neither Delcardayre, Peterson, nor Miao, alone or in any combination teach or suggest Applicants’ claimed method of mixing heterologous genes in expression cassettes located on artificial chromosomes.

As stated above, in order to establish a *prima facie* case of obviousness, the patent office must show that “the references must expressly or impliedly suggest the claimed invention” (MPEP 706.02(j)). Furthermore, Chapter 2143.01 of the MPEP states, “The mere fact that references can be combined or modified does not render the resultant combination obvious unless ****>**the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007); 82 USPQ2d 1385, 1396 (2007).”

As set forth in the above arguments, Delcardayre and Peterson fail to expressly or impliedly suggest the element of independent claim 1 that “rs₁ and rs₂ together comprise a rare restriction site...comprising a recognition sequence of 7 to 50 bases,” and Peterson teaches away from Applicants’ invention.

Miao does not remedy any of the deficiencies in the combined teachings of Delcardayre and Peterson and merely describes that an “intron may be used in [the] expression cassette” (see pending Action, p. 5). In view of these deficiencies, the result of any combination of teachings of Delcardayre, Peterson, and Miao would not have motivated a person of ordinary skill in the art to make and use the claimed invention with any expectation of success; thus, the combination of the cited references cannot be used as a basis for an obviousness rejection as asserted by the Office. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 58 under 35 USC § 103 based on Delcardayre in view of Peterson and further in view of Miao.

4. Rejection of claim 103 under 35 USC § 103 based on Delcardayre in view of Peterson and further in view of Smith

The Office has rejected claim 103 as obvious based on Delcardayre et al. (WO 98/31837) (“Delcardayre”) in view of Peterson et al. (US Patent No. 5,783,431) (“Peterson”), and further in view of Smith et al. (1990, *PNAS* 87: 8242-6) (“Smith”). Applicants respectfully disagree and traverse the rejection.

Neither Delcardayre, Peterson, nor Smith, alone or in any combination teach or suggest Applicants’ claimed method of mixing heterologous genes in expression cassettes located on artificial chromosomes.

As stated above, in order to establish a *prima facie* case of obviousness, the patent office must show that “the references must expressly or impliedly suggest the claimed invention” (MPEP 706.02(j)). Furthermore, Chapter 2143.01 of the MPEP states, “The mere fact that references can be combined or modified does not render the resultant combination obvious unless **>the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007); 82 USPQ2d 1385, 1396 (2007).”

As set forth in the above arguments, Delcardayre and Peterson fail to expressly or impliedly suggest the element of independent claim 1 that “rs₁ and rs₂ together comprise a rare restriction site...comprising a recognition sequence of 7 to 50 bases,” and Peterson teaches away from Applicants’ invention.

Smith does not remedy any of the deficiencies in the combined teachings of Delcardayre and Peterson and merely describes the “inclusion of a conditional centromere that can be turned on or off by changing the carbon source in the yeast artificial chromosome (YAC), which allows copy number amplification of the YAC” (see pending Action, p. 6). In view of these deficiencies, the result of any combination of teachings of Delcardayre, Peterson, and Smith would not have motivated a person of ordinary skill in the art to make and use the claimed invention with any expectation of success; thus, the combination of the cited references cannot be used as a basis for an obviousness rejection as asserted by the Office. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 103 under 35 USC § 103 based on Delcardayre in view of Peterson and further in view of Smith.

5. Rejection of claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 52, 54, 56-60, 62, 80, 102-104 under 35 USC § 112, first paragraph, enablement

The Office has rejected claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 52, 54, 56-60, 62, 80, 102-104 as allegedly lacking enablement under 35 USC § 112, first paragraph. In particular, the Office asserts that the specification, while being enabling for the claimed method using yeast or fungal cells as host, does not reasonably provide enablement for the claimed method in other cell types such as mammalian, vertebrate, plant, or insect cells. Applicants respectfully disagree and traverse the rejection.

As stated in Chapter 2164.01 of the MPEP:

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention....("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. (Emphasis added.)

The Office alleges on p. 8 of the Action that "the specification does not provide guidance for practicing the claimed method in host cells other than yeast or fungal cells. Therefore the breadth of the claim exceeds the teaching of the specification." More specifically, the Office asserts on p. 9 that:

The state of the art at the time of filing does not provide teaching for how to accomplish the mating for the purpose of mixing heterologous gene cassettes located on the artificial chromosome and subsequent selection and meiosis in cells other than yeast and fungal species. In fact the art teaches that the exchange of genetic material between cells such as mammalian, plant, insect, etc occurs through mechanism [*sic*] other than "mating." As such, whether the claimed method can be practice with any type of cell is unpredictable.

Applicants respectfully submit that independent claim 1 specifies that the cells should be able to "mate or fuse with each other," and thus that the claims are not limited only to those types of cells capable of "mating." Indeed, the specification at least at paragraphs [0035]-[0040] discloses certain aspects of the invention in which the cells are "cells that can be fused" and that such a method "may be used even in cases where it is not possible to mate cells in vitro." Additionally, the specification discloses prokaryotes and animal cells as examples of cell types that can be fused.

Cell fusion was well-known in the art at the time of filing. For example, Ruthe and Adler (1985, *Biochimica et Biophysica Acta* 819: 105-113) disclose fusion of genetically different bacterial spheroplasts, resulting in strains of bacteria possessing a combination of genetic markers. With regard to animal cells, Karsten et al. (1988, *Hybridoma* 7(6): 627-33) disclose that both electric fields and polyethylene glycol (PEG) can be used to fuse mammalian cells. Constabel (1976, *In Vitro* 12(11): 743-8) and Nakajima and Miyake (1978, *Somatic Cell Genet.* 4(2): 131-41) discloses PEG-induced fusion of plant cells and insect cells, respectively. These references are attached herewith.

As stated in the MPEP, “a patent need not teach, and preferably omits, what is well known in the art.” Given the knowledge of cell fusion in the art at the time of filing, the specification’s disclosure of aspects of the invention comprising cells that can be fused, and the recitations in independent claim 1 and claims dependent therefrom of both mating and fusion of cells, Applicants respectfully submit that the specification fully enables one of skill to make and use the claimed invention over its full scope without undue experimentation. In view of the above, Applicants respectfully request reconsideration and withdrawal of the 35 USC § 112, first paragraph rejections of claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 52, 54, 56-60, 62, 80, 102-104.

6. Conclusion

The applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited. If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned representative at 312-913-0001 in order to expedite prosecution.

Respectfully submitted,
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